The Diverse Diversity

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The human being is genomically similar to a chimpanzee, while phenotypically different.[1,2] Most of the differences are due to a relatively small number of changes in gene regulation, implying that small genomic differences may cause significant phenotypic diversities. Simple base-pair deletion at epidermal growth factor receptor (EGFR) exon 19 or single point mutation at *EGFR* exon 21 has dramatically shifted the treatment paradigm of patients with advanced non-small cell lung cancer. Most patients with the mutation will likely respond to EGFR tyrosine kinase inhibitor (TKI) such as gefitinib or erlotinib and benefit from a prolonged duration of progression-free survival.[3–5] EGFR TKI is now considered a standard first-line therapy for patients harboring the *EGFR* mutation. The key issue is to identify these patients in daily practice, thus population-based incidence rate will be an important guide to oncologists.

Helland et al.[6] reported in the current issue of *Journal of Thoracic Oncology* the *EGFR* mutation rate of 7.5% in Norwegian patients with resectable early-stage non-small cell lung cancer. This represents the first report from northern Europe. Authors chose to study the incidence on resected lung tumor to reduce sample bias. Their decision assures sufficient tumor sample for *EGFR* mutation analysis, but their result may not be directly comparable with other existing reports on *EGFR* mutations that were conducted in patients with advanced-stage disease. The truth is that the current clinical indication for EGFR TKI is for patients with stage IV lung cancer with EGFR mutation. We cannot assume the incidence of *EGFR* mutation in early-stage lung cancer to be representative of patients with advanced-stage disease.

Diversity in incidence of *EGFR* mutation may partly be explained by the diversity in population selection. The highest incidence of *EGFR* mutation reported in a white population was 35%, in which the study population included only adenocarcinoma and 38% of whom were never smokers.[7] In unselected white population, the incidence ranges from 4.5 to 16.6%.[8,9] Smoking history of the study population contributes to the incidence. The number of pack years of smoking is in reverse proportion to the frequency of mutations.[10] Patients with more than 15 pack-year tobacco consumption has a far lower chance of harboring *EGFR* mutation. Unfortunately, most of the population-based study only classified patient qualitatively as never, former, or current smoker and failed to include quantitative documentation on tobacco consumption. In the report by Helland et al., previous smoker was defined as having stopped smoking at least 1 year before surgery. This definition would have limited correlation with the chance of harboring *EGFR* mutation. A patient with 30 pack-year history of tobacco consumption and who quit over 1 year before would have much lower incidence than a patient with 10 pack-year history and quitted for the same duration. Authors included only 15 never smokers in the study population of 240 Norwegians and failed to report the national statistics on never smoker with lung cancer in their country. Expectedly, 8 (53%) of the 15 never smokers were positive for *EGFR* mutation. If more "never smokers" were included in the study population, the overall incidence would be higher than 7.5%. Therefore, the "apparent" ethnic-based incidence depends on proportion of never smokers in the study population.

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Diversity in testing methods may also explain the difference in incidence of *EGFR* mutation. Direct sequencing is considered the standard testing method. Nevertheless, sensitivity of the test is limited by the relative abundance of mutated allele versus the wild-type allele. False-negative rate is estimated at 10% pending on the quality of the tumor sample.[11] Other testing methods such as Scorpion ARMS (Therascreen *EGFR* mutation kit by DxS, Manchester, UK) or denaturing high-performance liquid chromatography are more sensitive, but the Scorpion Amplification Refractory Mutation System limits to 28 known mutations at the *EGFR* gene and may miss other mutations. Iressa Pan-Asia Study and First-line Single Agent Iressa versus Gemcitabine and Cisplatin Trial in Never-smokers with Adenocarcinoma of the Lung share similarity in study population including only Asian nonsmokers with adenocarcinoma, but the incidence of *EGFR* mutation was 59.7% (261/437) and 43.8% (42/96), respectively.[3,12] The 16% difference could be explained by the different testing method. Iressa Pan-Asia Study used Scorpion ARMS, and tumor response rate to gefitinib in patients without *EGFR* mutation was 1.1%, suggesting a very low false-negative rate. First-line Single Agent Iressa versus Gemcitabine and Cisplatin Trial in Never-smokers with Adenocarcinoma of the Lung used direct sequencing, and 7 (25.9%) of 27 mutation "negative" patients responded to gefitinib. The high tumor response rate in their mutation-negative patient is best explained by false-negative rate of the testing method, and the false-negative rate explained the difference in incidence of the two study populations.

Rate is a ratio of two measurements. Difference in rate between two populations will have little meaning if measurements of the denominators are not the same. In comparison of *EGFR* mutation rate between ethnicity, it is essential to assure the study populations sharing the same proportion of adenocarcinoma, tobacco consumption, and testing methods. The observation of a higher *EGFR* mutation rate in East Asian is likely a true phenomenon, but the smaller variations between other ethnicities could be explained by diversities in the study populations.

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